REMARKS

Title.

The title is amended to more clearly identify the subject matter of this divisional after the restriction requirement has been entered. A redlined page is provided to show this amendment.

Claims.

The claims present in this divisional application are claims 1-46, with claims 1-31, 37, 40, 42 and 43 withdrawn from consideration and claims 32-36, 38-39, 41, and 44-46 presently rejected. Applicants' request that claims 1-31 be cancelled.

To ensure better understanding with respect to the present claims, some general information concerning the present elements in the claims is provided.

The term "platinum containing compound" is defined on page 9, lines 5-17. The platinum containing compound must be of a type that can ~~reversibly~~ conjugate to the functional groups of the dendritic polymer and have anti-tumor activity. Examples include platinum containing compounds having a tetravalent platinum atom bonded to the nitrogen of two amine ligands (which may be different) in a cis conformation and at least one of the remaining ligands interacting or displacing a functional group of the dendritic polymer. Specific examples mentioned are cis-diamminedichloroplatinum (cisplatin) and its various analogues.

Platinum is the element Pt, atomic number 78, Group VIII. There are six naturally occurring isotopes: 190 (radioactive with $T_{1/2} = 6.9 \times 10^{11}$ years); 192; 194; 195; 196; 198. According to the Merck Index, Eleventh Edition, 1989, Pt is insoluble in water and single mineral acids. It reacts with boiling aqua regia forming chloroplatinic acid and molten alkali cyanides. Inhalation of dust of soluble platinum salts is irritating and may cause more disorders in humans. Thus the zero valence Pt metal would not be suitable to be used in this invention; whereas the metals named in the cited Patent, US 5,338,532, were able to be used although for a different utility. This is a significant distinction in the properties of Pt vs. Y or lanthanide metals.

The preferred platinum containing compound is described generally in the same Merck Index as follows. Cisplatin is (SP-4-2)-diamminedichloroplatinum,

$Cl_2H_6N_2Pt$, is a tetraplatinate structure of $Cl_2(NH_3)_2Pt$, and is soluble in water and DMF, but insoluble in most common solvents. This cisplatin compound is the presently preferred embodiment, and its possible analogues, for the term "platinum containing compound".

Some cisplatin analogues are listed in the Merck Index as Platiblastin [Farmitalia], Platinex [Bristol], Platinol [Bristol], Platinoxan [Degussa], Platistin [Farmitalia], Platosin [Nordic], and Cis-Platinum II. The bracketed names are companies that sell the compound. The use given is antineoplastic for all such compounds.

In reviewing that Merck Index, which contains information on *chemicals, drugs, and biological substances*, the following Pt compounds were found which are indicated as soluble in water to some degree, but none of them have any known therapeutic use, including on treatment of malignant tumors.

- Platinic Ammonium Chloride, $Cl_6H_8N_2Pt$, is slightly soluble in water and insoluble in alcohol.
- Platinic Chloride, Cl_6H_2Pt, is a hexahydrate that is soluble in water and alcohol.
- Platinic Iodide, PtI_4, is soluble in water.
- Platinic Potassium Chloride or Potassium Hexachloroplatinate (IV), Cl_6K_2Pt, is soluble in hot water and insoluble in alcohol.
- Platinous Ammonium Chloride, $Cl_4H_8N_2Pt$, is soluble in water.
- Platinic Potassium Thiocyanate or Potassium Hexathiocyanatoplatinate (IV), $C_6K_2N_6PtS_6$, is soluble in water.
- Platinous Barium Cyanide or Barium Platinous Cyanide, C_4BaN_4Pt, is soluble in water, is a poison.
- Platinous Chloride, Cl_2Pt, is insoluble in water, alcohol and ether. Soluble in HCl. Will combine with PCl_3 to form a compound soluble in benzene or chloroform.
- Platinous Iodide or Platinum Diiodide, I_2Pt, is insoluble in water or alkali iodides.

- Platinous Lithium Cyanide, $C_4Li_2N_4Pt$, pentahydrate, is slightly soluble in water.
- Platinous Potassium Chloride or Potassium Tetrachloroplatinate (II), Cl_4K_2Pt, is soluble in water.
- Platinous Potassium Cyanide or Potassium Tetracyanoplatinate (II), $C_4K_2N_4Pt$, is soluble in hot water.
- Platinous Thorium Cyanide or Thorium Tetracyanoplatinate (II), $C_8N_8Pt_2Th$, is sparingly soluble in water.
- Platinum Dioxide or Platinic Oxide, O_2Pt, is a catalyst in hydrogenation.

It is clear that not many Pt compounds are used for therapeutic purposes, but are rather included as chemicals for the Index. No Pt compound with a dendrimer is discussed as commercially available.

The dendritic polymer platinates are prepared as described from page 9, line 18, through page 10, line 2. Because cisplatin and the selected dendrimer are both water soluble, the dendritic polymer platinates can be prepared as described in the specification and shown by Example 5. The ratio of cisplatin to dendrimer is about 100:1 to about 1:1, preferably about 35:1 (see page 9, lines 22-27). Thus the loading of platinum per dendrimer can be very high and is preferred to the presently available, commercial cisplatin delivery systems where no polymer carrier is present. The present conjugate reduces the toxic effects of the cisplatin to such an extent that a much higher dose of cisplatin is delivered.

The dendritic polymer platinates must have "a therapeutic effect on malignant tumors" as described on page 10, lines 3 through 21. Applicants have provided the test results for that purpose in the examples, *e.g.*, Examples 9A, 9B, 10, 11,12, and 13. Thus Applicants have support for these elements in their claims.

This delivery system as now claimed is much needed for this platinum drug family. A presently sold cisplatin analogue – platinum, diamine [1,1-cyclobutane-dicarboxylato(2-)-0,0']-,(SP-4-2) with the empirical formula $C_8H_{12}N_2O_4Pt$ sold under the trademark Paraplatin [Bristol] – has warnings that its use requires adequate treatment facilities be available for administration as bone marrow suppression is dose

related and can be severe, anemia may be cumulative and require transfusion, vomiting is frequent. Platinol-AQ [Bristol] is cisplatin for injection, where renal toxicity is common and severe as well as myelosupression, nausea and vomiting. Some ototoxicity with loss of hearing and deafness is significant. [These warnings are from Physicians' Desk Reference, 2001.] In contrast, the present conjugates exhibit high drug efficiency, high drug carrying capacity (high loading of active drug in the dendritic polymer carrier), good water solubility, good stability on storage, reduced toxicity, and improved anti-tumor activity *in vivo*. These features of the present conjugate are important and could not be ascertained or predicted until the conjugate was made and tested.

Rejection under 35 USC §103(a)

Claims 32-36, 38, 39, 41, 44-46

as unpatentable over US Patent 5,338,532 (Tomalia *et al.*)

With regard to obviousness of the present invention over the cited US Patent 5,338,532 (US '532 Patent), Applicants provide the following remarks.

US '532 Patent is directed to using various dendrimers as carriers for a variety of materials. The materials can be carried by the dendrimer either on its surface, in its interior or on both its surface and interior. The only exemplified metals (as zero valence metals, or as ionic or radioactive metals) in the cited patent are:

USSN 09/881,126

'532 Example No.	Metal	Dendrimer
5	iron (Fe)	PAMAM 6.0, sodium propionate terminated
6	rhodium (Rh)	PAMAM 2.5, ester terminated
7	palladium (Pd)	PAMAM 3.5, ester terminated
8	90-yttrium (^{90}Y)	PEI 2.0, methylenecarboxylate terminated
10	yttrium (Y)	PAMAM 2.0, methylenecarboxylate terminated
13	111-indium (^{111}In)	PAMAM 3.0, methylenecarboxylate terminated
19	lead (Pb)	PAMAM 10.0
22	manganese (Mn)	PAMAM 3.0, ester terminated
23	iron (Fe)	PAMAM 6.0, sodium
24	gadolinium (Gd)	PAMAM 2.0, acetate terminated PEI 2.0, acetate terminated

Clearly, platinum (Pt) is not specifically taught in any of the Examples of the US '532 Patent, although it would be included within its general teachings and generic claims, but not its specific claims. Cisplatin, its analogues, or the use of a central tetravalent platinum atom in a platinum containing compound are not described.

Platinum has several unique properties, which make prediction of its use difficult. As a metal it is only soluble in aqua regia which for pharmaceutical applications would not be desired. It is insoluble in most pharmaceutically desirable solvents. Thus getting a solution of the metal for the claimed utility is not pharmacologically possible. As can be seen from the above general discussion of platinum compounds, they are not known for such therapeutic utility in general and are sparingly soluble in water. Thus one skilled in the art would not have much experience in using platinum containing compounds for therapeutic applications and therefore little motivation to use platinum for the present purpose.

As of the priority filing date for the instant parent application, cisplatin was known for the present utility and dendrimer carriers were known. However, Applicants contend that to try to put these two elements together in a drug delivery system for the method of the present claims was not predicable or likely to occur to

one skilled in this art because of no knowledge as to success of stability, retaining activity of the drug when delivered, l wering toxicity from that of injected cisplatin, or amount of loading of active in the dendrimer could not be predicted. Also no drug carriers for Pt or cisplatin were commercial to use as a guide to provide knowledge of the claimed method.

Some of the advantages with the present conjugate used in the claimed method as a pharmaceutical delivery system is that it has greater reliability to deliver the proper dose of active drug and is administered in a form having lower side effects and better rate of delivery. This result could not be foretold. Drug delivery for dose and release in this system for a metal that is not used widely in a variety of applications could not be assumed. An "obvious to try" is not the standard test for patentability. There is no suggestion for combining these two elements (dendrimer with cisplatin or platinum compound) by any statements found in this cited US '532 Patent. Thus the only reason for the present combination of these elements is use of hindsight by reading the present specification. Also an "obvious to try" to combine elements is not an acceptable standard for rejection. There is no way to predict whether such combination of elements would work for the intended purpose. The Examiner has provided no basis for the combination of these particular elements, other than reading the present claims. The invention as claimed is not taught by the cited US '532 Patent.

The Examiner has cited no recitation of a suggestion in the cited US '532 Patent and no specific principle known to one of ordinary skill in the art that would have guided the skilled artisan to select the particular combination of dendritic polymer and platinum containing compound, such as the tetravalent platinum or cisplatin, to use in the method of the present claims. Even though these two components were known, the advantages and reasons to combine were not known, and one skilled in the art would have had no reason to know if such combination would be effective to maintain the utility of the drug, release it at the proper time, have less toxicity as a conjugate, and permit sufficient dose to be delivered. The specific properties of platinum make it difficult to determine what will be successful. The use of other compounds as metals (described hereinabove) for conjugation to

dendrimers provides little guidance to one skilled in the art for how to use platinum compounds, which ones, the valance state, the toxicity, the dose, and many other factors which were not known and not predictable. As the Federal Circuit has stated in In re Rouffet (149 F.3d 1350 (1998)),

> . . . [A]n examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 U.S.P.Q.2D (BNA) 1551, 1554 (Fed. Cir. 1996).
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed.

Also see In re Dembiczak (175 F.3d 994 (Fed. Cir. 1999)). Thus, because no specific reasons for combining the particular elements of the presently claimed invention or reason to use such combination in the claimed method have been recited in the rejection, Applicants believe that a *prima facie* showing of obviousness of the invention as presently claimed has not been made. Applicants believe that these amendments and remarks overcome the rejections and respectfully request that they be removed.

The present invention describes a process for making the platinum chelate with the dendrimer in a suitable form so that it is useful for delivery. Applicants have shown a process of preparing this conjugate (see page 9, lines 18-30 and page 10, line 25 through page 11, line 9) and that the dendrimer conjugate with platinum retains its effectiveness (see pages 11-23). This process allows for the solubility of cisplatin, the order of addition and controlled conditions to form the conjugate used in the claimed method. The conjugate may be very large – 44 nm in diameter whereas the dendrimer is 4 nm in diameter. Thus this present conjugate is much larger than a complex of Y with a dendrimer (cited in the Action) or other metals described in the cited US '532 Patent. The conditions must be carefully controlled (*e.g.*, rate of addition, time, and

temperature). As these conditions are not those described by the cited US '532 Patent and such combination was not taught in the cited art (except by hindsight from these present claims), Applicants believe that they are entitled to the present claims as a selection invention over the US '532 Patent (both applications are assigned to the same company).

Although Applicants realize that these present claims are dominated by the cited US '532 Patent teachings, no adequate process for preparing these presently claimed conjugates was provided because of platinum's solubility issues and order of adding the components to control size, nor could the activity of the conjugate to maintain the use and efficacy of the active drug be predicted as often any change of the delivery system adversely effects the activity of the drug. The present conjugate has the desired advantages of delivery of a platinum conjugate with a dendritic polymer while maintaining the desired use.

Additionally, the present dendritic conjugate has a much higher delivery of the dose of platinum compound to the patient in less volume than the present commercial drug delivery systems. This is an important factor in patients that have ovarian cancer for effective, high dose therapy. See for example, page 9, line 24 through page 10, line 13. Thus the Applicants respectfully request the removal of the present rejection and allowance of claims 32-46 as now presented.

CONCLUSION

Applicants believe that all objections and rejections presented in the Office Action mailed March 17, 2003 have been overcome by this Response. Applicants respectfully request that the rejections and objections be reconsidered in light of these remarks and amendments and that the rejected claims 32-36, 38, 39, 41 and 44-46 together with withdrawn claims 37, 40, 42 and 43 be allowed.

USSN 09/881,126

Applicants request that if there are issues remaining unresolved regarding any points raised by this Action or that if no claims are found allowed after consideration of this response, that an interview be granted at a mutually convenient time either by telephone or in person.

Respectfully submitted,

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